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REVIEW

Functional anatomy of 5-HT$_{2A}$ receptors in the amygdala and hippocampal complex: relevance to memory functions

Cristiano Bombardi · Giuseppe Di Giovanni

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Abstract The amygdaloid complex and hippocampal region contribute to emotional activities, learning, and memory. Mounting evidence suggests a primary role for serotonin (5-HT) in the physiological basis of memory and its pathogenesis by modulating directly the activity of these two areas and their cross-talk. Indeed, both the amygdala and the hippocampus receive remarkably dense serotoninergic inputs from the dorsal and median raphe nuclei. Anatomical, behavioral and electrophysiological evidence indicates the 5-HT$_{2A}$ receptor as one of the principal postsynaptic targets mediating 5-HT effects. In fact, the 5-HT$_{2A}$ receptor is the most abundant 5-HT receptor expressed in these brain structures and is expressed on both amygdalar and hippocampal pyramidal glutamatergic neurons as well as on γ-aminobutyric acid (GABA)-containing interneurons. 5-HT$_{2A}$ receptors on GABAergic interneurons stimulate GABA release, and thereby have an important role in regulating network activity and neural oscillations in the amygdala and hippocampal region. This review will focus on the distribution and physiological functions of the 5-HT$_{2A}$ receptor in the amygdala and hippocampal region. Taken together the results discussed here suggest that 5-HT$_{2A}$ receptor may be a potential therapeutic target for those disorders related to hippocampal and amygdala dysfunction.

Keywords Amygdala · Hippocampal region · 5-HT$_{2A}$ receptor · Principal neurons · Interneurons · Serotonin · Emotional memory · Learning

C. Bombardi (✉)
Department of Veterinary Medical Science, University of Bologna, 40064 Ozzano dell'Emilia, Bologna, Italy
e-mail: cristiano.bombardi@unibo.it

G. Di Giovanni (✉)
Neuroscience Division, School of Biosciences, Cardiff University, Life Sciences Building, Museum Avenue, Cardiff CF10 3AX, UK
e-mail: digiovannig@cardiff.ac.uk

G. Di Giovanni
Department of Physiology and Biochemistry, Faculty of Medicine and Surgery, University of Malta, Tal-Qroqq, Malta

Introduction

The amygdaloid complex (or amygdala) and the hippocampal region are part of the temporal lobe. These regions, interconnected by many reciprocal pathways (Pikkarainen et al. 1999; Pikkarainen and Pitkänen 2001; Kemppainen et al. 2002; Pitkänen et al. 2002; Majak and Pitkänen 2003), mediate functions involving emotion and memory (Aggleton 2000; Morris 2007; Whalen and Phelps 2009). The amygdala and the hippocampus region are linked to two independent memory systems, but they act in concert when "emotion meets memory" (Phelps 2004). The amygdala has an essential role in the expression of emotions and the formation of emotion-related memories (LaBar and Phelps 1998). The hippocampus instead is involved in the storage of explicit/declarative memory (Eichenbaum et al. 1996). These two brain areas affect each other in subtle but important ways (Richardson et al. 2004). Indeed, the amygdala influences both the encoding and the storage of hippocampal-dependent episodic memory for emotional stimuli. On the other hand, the hippocampus can influence the amygdala response when emotional stimuli are encountered, by enabling it to place the event into the proper context (Phelps 2004).

Among all the neurotransmitters, serotonin (5-hydroxytryptamine, 5-HT) seems to play a critical role in the

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regulation of the various amygdala/hippocampal functions (Pralong et al. 2002; Harvey 2003; Hensler 2006). Moreover, many neurological and psychiatric diseases, especially affective disorders, are characterized by a serotonergic dysfunction in these regions (Pralong et al. 2002; Hensler 2006; Shin et al. 2006; Esposito et al. 2008, Di Giovanni et al. 2011). Among the plethora of 5-HT receptors (Rs), 5-HT_{2A}Rs have received considerable attention because of their distribution in these areas, relative high affinity for atypical antipsychotics, and their involvement in the etiology of psychiatric diseases (Gray and Roth 2001; Meltzer and Huang 2008) and memory impairments (de Quervain et al. 2003). Moreover, serotonergic innervations of the amygdala and the hippocampus have been shown to mediate anxiogenic effects by 5-HT_{2A}Rs stimulation (Graeff and Zangrossi 2010). Finally, reduced 5-HT_{2A} receptor signaling has been found in the amygdalae (Hurlemann et al. 2009) and hippocampi (Mintun et al. 2004) of patients suffering from anxiety and depression, respectively.

Serotonin interacts with various subtypes of receptors, which have different cellular and subcellular distribution in the central nervous system (CNS). Based on molecular and pharmacological properties, serotonin receptors are classified into 7 families (from 5-HT_1 to 5-HT_7), which comprise 14 receptor subtypes. Most serotonin receptors are typically G-protein coupled, besides the 5-HT_3 receptor that is a ligand ion channel (Barnes and Sharp 1999; Hoyer et al. 2002).

The 5-HT_2 receptor (5-HT_2R) family comprises the 5-HT_{2A}, 5-HT_{2B}, and 5HT_{2C} receptors, which exhibit 46–50 % overall sequence identity and couple preferentially to Gq/11 to increase inositol phosphates and cytosolic Ca^{2+} (Di Giovanni et al. 2006). The 5-HT_{2A}R comprises 471 amino acids and presents seven transmembrane domains. This serotonin receptor also activates phospholipase D and phospholipase A2 by interacting with additional G-proteins (Barnes and Sharp 1999; Hoyer et al. 2002). In a variety of brain regions, 5-HT_{2A}R activation results in neuronal depolarization because of the decrease in potassium conductance (Barnes and Sharp 1999; Hoyer et al. 2002). Stimulation of the 5-HT_{2A}R also increases cGMP production through an indirect cellular mechanism involving glutamate release and N-methyl-D-aspartate (NMDA) receptor activation (Regina et al. 2004). There is generally an overlap between the distribution of 5-HT_{2A}R mRNA and immunoreactivity, suggesting a postsynaptic location (Lopez-Gimenez et al. 2001).

The aim of the present review is to summarize what is known about the functional distribution and the role of 5-HT_{2A}Rs in modulating amygdaloid complex and hippocampal activity in relation to emotional memory.

Anatomical organization of the amygdala

The amygdala is an anatomically heterogeneous structure located in the temporal lobe that comprises 13 nuclei and cortical areas and their subdivisions (Pitkänen 2000; Pitkänen and Kemppainen 2002). Cytoarchitectonic, chemoarchitectonic, and connectional analysis of the amygdala in the rat and monkey indicate that this structure is composed of deep, superficial, and "remaining" nuclei (Table 1; Pitkänen 2000; Pitkänen and Kemppainen 2002).

Consistent with the anatomic heterogeneity, multiple functions are assigned to the amygdala, including generation of emotional responses, formation of emotional memories, enhancement of explicit memory formation in emotionally arousing situations, formation of stimulus-reward associations, and regulation of sexual behavior (Aggleton 2000; Whalen and Phelps 2009). Alterations in the amygdaloid functions can occur in neurological and psychiatric diseases such as Alzheimer's disease, temporal lobe epilepsy, schizophrenia, anxiety, and depression (Aggleton 2000; Whalen and Phelps 2009).

Major cell types of the amygdala

Different morphological, immunohistochemical, and physiological studies have showed that different cell types are distributed in the amygdaloid complex (Table 1; McDonald 1992, 1998; Sah et al. 2003; Spampanato et al. 2011). The deep nuclei exhibit two major cell classes: excitatory (glutamatergic) pyramidal projection neurons and inhibitory (γ-aminobutyric acid [GABA]ergic) nonpyramidal interneurons. The pyramidal neurons have conical cell bodies and five to seven spiny primary dendrites. GABAergic interneurons are a heterogeneous population of sparsely spiny or nonspiny neurons that can be divided into distinct subpopulations on the basis of their content in calcium-binding proteins and peptides (for reviews, see McDonald 1992, 1998; Sah et al. 2003; Spampanato et al. 2011). In the superficial nuclei, the two main cell types are pyramidal and nonpyramidal neurons (McDonald 1992, 1998; Sah et al. 2003). Although these cells exhibit a laminar organization (layers I, II, and III), their morphology is similar to those of counterparts in the deep nuclei. Thus, pyramidal neurons are excitatory projection neurons that utilize glutamate as an excitatory neurotransmitter, whereas nonpyramidal neurons are local circuit cells that utilize GABA as an inhibitory neurotransmitter (McDonald 1992, 1998; Sah et al. 2003). Unlike other superficial amygdaloid nuclei, the medial nucleus contains small-to medium-sized ovoid neurons which possesses moderately to densely spiny dendrites (McDonald 1992, 1998; Sah et al. 2003). In the anterior

Table 1 Nuclei, nuclear subdivisions, and cell types of the rat and monkey amygdala

Nuclei	Rat subdivisions	Monkey subdivisions	Cell types
Deep nuclei			
Lateral nucleus	Dorsolateral	Dorsal	Pyramidal and nonpyramidal neurons
	Medial	Dorsal intermediate	
	Ventrolateral	Ventral intermediate	
		Ventral	
Basal nucleus	Magnocellular	Magnocellular	
	Intermediate	Intermediate	
	Parvicellular	Parvicellular	
Accessory basal nucleus	Magnocellular	Magnocellular	
	Parvicellular	Parvicellular	
		Ventromedial	
Paralaminar nucleus	–	No subdivisions	
Superficial nuclei			
Bed nucleus of the accessory olfactory tract	No subdivisions	–	Small spherical, angular, and fusiform neurons
Medial nucleus	Rostral	No subdivisions	Small-to-medium-sized ovoid neurons
	Central (dorsal and ventral parts)		
	Caudal		
Nucleus of the lateral olfactory tract	No subdivisions	No subdivisions	Pyramidal and nonpyramidal neurons
Anterior cortical nucleus	No subdivisions	No subdivisions	
Periamygdaloid cortex (PAC)	Periamygdaloid cortex	PAC oral	
	PAC medial	PAC1	
	PAC sulcal	PAC2	
		PAC3	
		PAC sulcal	
Posterior cortical nucleus	No subdivisions	No subdivisions	
Remaining nuclei			
Anterior amygdaloid area	No subdivisions	No subdivisions	Spiny projection neurons and nonspiny interneurons
Central nucleus	Capsular	Lateral	Medium-sized ovoid spiny neurons and ovoid, fusiform, and piriform, sparsely spiny neurons
	Lateral	Medial	
	Intermediate		
	Medial		
Intercalated nuclei	No subdivisions	No subdivisions	Medium ovoid neurons with spiny dendritic trees and large cells with very long thick spiny or aspiny dendrites
Amygdalohippocampal area	Lateral	Dorsal	Pyramidal and nonpyramidal neurons
	Medial	Ventral	

amygdaloid area, there are small-to-medium-sized ovoid, fusiform, or polygonal densely spiny projection neurons and nonspiny interneurons (McDonald 1992, 1998; Sah et al. 2003). The neuronal morphology of the amygdalohippocampal area is virtually similar to that described for the deep nuclei (McDonald 1992, 1998; Sah et al. 2003). Central nucleus has neurons very different from those present both in deep and in superficial nuclei. The lateral division of the central nucleus exhibits a homogeneous population of medium-sized ovoid spiny neurons which resemble those of the caudato-putamen. The vast majority of the neurons in the capsular division of the central nucleus are similar to those in the lateral division. The medial division of the central nucleus is composed mainly of ovoid, fusiform, and piriform, sparsely spiny neurons (McDonald 1992, 1998; Sah et al. 2003). Finally, in the intercalated nuclei, there are two main types of neurons: medium ovoid neurons with spiny dendritic trees and large cells with very long thick

spiny or aspiny dendrites (McDonald 1992, 1998; Sah et al. 2003). Central nucleus and intercalated nuclei are almost entirely populated by GABAergic neurons that act not only as local circuit cells, but also as projection neurons (McDonald 1992, 1998; Sah et al. 2003).

Anatomical organization of the hippocampal formation

The hippocampal region consists of two sets of cortical structures, the hippocampal formation and the parahippocampal region (Scharfman et al. 2000; Witter and Amaral 2004). The hippocampal formation is composed of three-layered allocortical structures, including the dentate gyrus (DG), the hippocampus proper (which is subdivided into three fields: CA3, CA2 and CA1), and the subiculum (Scharfman et al. 2000; Witter and Amaral 2004). The parahippocampal region, located between the neocortex and the hippocampal formation, includes the presubiculum, the parasubiculum, the entorhinal cortex, the perirhinal cortex, and the postrhinal cortex (in nonprimate mammalian species) or parahippocampal cortex (in primates) (Scharfman et al. 2000; Witter and Amaral 2004). The parahippocampal region consists of two six-layered cortices called the periallocortex and the proisocortex. The periallocortex is characterized by the presence of an acellular layer IV (termed *lamina dissecans*) and includes the presubiculum, the parasubiculum, and the entorhinal cortex (Scharfman et al. 2000; Witter and Amaral 2004). The perirhinal and postrhinal cortices are proisocortical structures in which the *lamina dissecans* disappears and layer IV is not as well developed as that in the neocortex (Scharfman et al. 2000; Witter and Amaral 2004).

The hippocampal formation plays a prominent role in spatial learning and declarative memory (Morris 2007). The parahippocampal region has a pivotal position between the neocortex and the hippocampal formation and relays the majority of the hippocampal formation input and output, in particular via the entorhinal cortex (Witter and Amaral 2004).

Major cell types of the hippocampal formation

In the hippocampal region, there are several subpopulations of neurons that can be distinguished on the basis of their morphology and neurochemical code, as well as their connections and electrophysiological characteristics (Amaral and Lavenex 2007; Witter and Amaral 2004). Although the neuronal and synaptic organization is extremely complex, the cell types of the entire hippocampal region can be classified in two main groups: principal excitatory (glutamatergic) projection neurons and inhibitory (GABAergic) interneurons (Amaral and Lavenex 2007; Witter and Amaral 2004). The principal neurons are represented by granule cells of the DG and pyramidal cells of the hippocampus proper, the subiculum, the presubiculum, the parasubiculum, the entorhinal cortex, the perirhinal cortex, and the postrhinal cortex (Amaral and Lavenex 2007; Witter and Amaral 2004). The granule cell has a small elliptical cell body and a cone-shaped tree of spiny dendrites. Pyramidal cells have a pyramidal-shaped cell bodies from which arise a basal and an apical spiny dendritic tree (Amaral and Lavenex 2007; Witter and Amaral 2004). GABAergic interneurons are a heterogeneous group of cells that can be characterized on the basis of their morphological and neurochemical features (for reviews, see Freund and Buzsáki 1996; Amaral and Lavenex 2007; Witter and Amaral 2004).

Serotonergic innervation of amygdala and hippocampal region

Tracing studies have demonstrated that serotoninergic inputs to the amygdala originate mainly from the dorsal raphe and, to some extent, from the median raphe nuclei (for reviews, see Pralong et al. 2002; Hensler 2006). The distribution of serotonin has also been detected in the amygdala with histofluorescence, radioautographic, and immunohistochemical procedures (Steinbusch 1981; Pralong et al. 2002; Bauman and Amaral 2005; Hensler 2006). The amygdala is densely innervated by serotonin immunoreactive (IR) fibers. However, substantial variation in fiber density is present among rodents and primates. In fact, in the rat amygdala, the lowest fiber densities are observed in the superficial and central nuclei. Low to moderate fiber densities are found in the parvicellular division of the basal nucleus and accessory basal nucleus. Moderate to high fiber densities are located in the lateral nucleus. The highest density of serotonin-IR fibers is observed in the magnocellular division of the basal nucleus and amygdalohippocampal area (Steinbusch 1981). On the other hand, in the monkey's amygdala, the density of serotonin-IR terminals is as follows: (i) low in the accessory basal, anterior cortical, posterior cortical and medial nuclei, and in subregions of the periamygdaloid cortex; (ii) moderate in portions of the basal, lateral, and intercalated nuclei; and (iii) high in the central nucleus, the nucleus of the lateral olfactory tract, the paralaminar nucleus, the anterior amygdaloid area, and a small region of the amygdalohippocampal area (Bauman and Amaral 2005). Accordingly, ultrastructural analyses in the rat basal nucleus (magnocellular and intermediate divisions) have demonstrated that serotonin terminals contact pyramidal and nonpyramidal (parvalbumin [PV]–IR and vasoactive intestinal peptide [VIP]–IR) neurons (Muller et al. 2007b).

The hippocampal region receives a robust serotoninergic innervation from the median and dorsal raphe nuclei (for reviews, see Pralong et al. 2002; Witter and Amaral 2004; Hensler 2006; Amaral and Lavenex 2007). In the hippocampal formation, the density of serotonergic fibers is higher in the DG and CA3 field than in the CA1 field and subiculum. Serotonin fibers directed to DG and hippocampus proper innervate especially GABAergic interneurons with axons that contact the distal dendrites of principal cells (granule and pyramidal cells) (Witter and Amaral 2004; Amaral and Lavenex 2007). In the presubiculum, parasubiculum and entorhinal cortex serotonin fibers innervate all layers, with the highest innervation in superficial layers (for reviews, see Pralong et al. 2002; Witter and Amaral 2004; Hensler 2006; Amaral and Lavenex 2007).

In the amygdala and hippocampal region, serotonin operates via conventional synapses as well as local volume neurotransmission, reaching their specific receptors through extra-cellular or paracrine diffusion (Amaral and Lavenex 2007; Muller et al. 2007b).

Functional distribution of the 5-HT_{2A} receptor in the amygdala

Deep nuclei

Different immunohistochemical studies have reported that the deep nuclei of the rat amygdaloid complex contain 5-HT_{2A}R–IR pyramidal and nonpyramidal neurons (Morilak et al. 1993; Cornea-Hébert et al. 1999; Xu and Pandey 2000; McDonald and Mascagni 2007; Jiang et al. 2008; Bombardi 2011). These studies correlate with the evidence from an in situ hybridization study showing that 5-HT_2R mRNA is located in the lateral, basal, and accessory basal nuclei (Wright et al. 1995). It is important to underline that other similar studies were contradictory; in fact, Pompeiano et al. (1994) failed to find 5-HT_{2A}R mRNA in the deep nuclei. Also, autoradiographic research has demonstrated specific binding in the deep nuclei, and specifically in the lateral nucleus (Pazos et al. 1985).

In the deep amygdaloid nuclei, virtually all of pyramidal cells express the 5-HT_{2A}R which appear to be prevalently located in the dendritic processes, especially apical dendrites (McDonald and Mascagni 2007; Bombardi 2011). Accordingly, the local injection of 1-(2,5-dimethoxy-4-iodophenyl)-2-aminopropane (DOI), a 5-HT_{2A}/5-HT_{2C} agonist, increases discharge rate (Stein et al. 2000) and facilitates synaptic plasticity via an NMDA-mediated mechanism (Chen et al. 2003) in presumptive pyramidal neurons of the rat basolateral amygdala.

Also, inhibitory nonpyramidal neurons in the rat deep nuclei express the 5-HT_{2A}R (Morilak et al. 1993; McDonald and Mascagni 2007; Bombardi 2011). In addition, double-immunofluorescence experiments have revealed that this receptor is expressed by 66.3, 70.6, and 66.4 % of the GABAergic neurons in the lateral nucleus, basal nucleus, and accessory basal nucleus, respectively (Bombardi 2011). It is important to point out that some differences in the degree of colocalization of GABA and the 5-HT_{2A}R have been observed in the various subdivisions of the basolateral amygdala. In particular, the highest percentages of GABAergic neurons expressing the 5-HT_{2A}R have been located in the medial subdivision of the lateral nucleus (74.7 %) and in the parvicellular and magnocellular subdivisions of the basal nucleus (73.8 and 71.9 %, respectively). The lowest percentage of double-labeled cells is located in the ventrolateral subdivision of the lateral nucleus (53.8 %) (Bombardi 2011). This variability suggests that the GABA release mediated by the 5-HT_{2A}R varied in the different subdivisions of the basolateral amygdala (Bombardi 2011). In the lateral (medial subdivision) and basal (magnocellular subdivision) nuclei of the rat amygdala, GABAergic neurons immunopositive for the 5-HT_{2A}R also express PV and somatostatin (SOM) (McDonald and Mascagni 2007). In particular, 59.8 % of PV–IR neurons in the lateral nucleus (medial subdivision) and 75.6 % of PV–IR neurons in the basal nucleus (magnocellular subdivision) express the 5-HT_{2A}R (McDonald and Mascagni 2007). In contrast, only 33.1 % of SOM–IR neurons in the lateral nucleus (medial subdivision) and 32.6 % of SOM–IR neurons in the basal nucleus (magnocellular subdivision) exhibit the 5-HT_{2A}R (McDonald and Mascagni 2007). Also, electrophysiological studies have demonstrated that the 5-HT_{2A}R activates GABAergic nonpyramidal neurons of the deep nuclei. In fact, α-methyl-5-hydroxytryptamine, a 5-HT_2R agonist, induces a dose-dependent membrane depolarization in the GABAergic interneurons of the rat basal nucleus (Rainnie 1999). Likewise, activation of the 5-HT_{2A}R enhances frequency and amplitude of spontaneous inhibitory postsynaptic currents (sIPSCs) recorded from pyramidal neurons located in the juvenile rat basolateral amygdala (Jiang et al. 2008). Accordingly, the inhibition of pyramidal cell firing in the lateral nucleus of the rat amygdala obtained after local application of serotonin is blocked by a simultaneous application of GABA antagonist (Stutzmann and LeDoux 1999). Finally, the activation of GABAergic nonpyramidal neurons of the rat basolateral amygdala is also induced by DOI (Stein et al. 2000; Sokal et al. 2005).

In the rat basal nucleus and along the external and internuclear borders of the rat basolateral amygdala, the 5-HT_{2A}R is also expressed by large GABAergic nonpyramidal neurons that project to the mediodorsal thalamus (McDonald and Mascagni 2007).

Superficial nuclei

Several immunohistochemical studies have reported 5-HT_{2A}R–IR neurons in the rat superficial nuclei (Morilak et al. 1993; Cornea-Hébert et al. 1999; Bombardi 2011). In particular, a high density of 5-HT_{2A}R–IR neurons is located in the nucleus of the lateral olfactory tract and in the bed nucleus of the accessory olfactory tract (Cornea-Hébert et al. 1999; Bombardi 2011). In situ hybridization investigations have demonstrated a moderate density of 5-HT_2R mRNA (Wright et al. 1995) and 5-HT_{2A}R mRNA (Pompeiano et al. 1994) in the rat superficial nuclei, with the exception of the bed nucleus of the accessory olfactory tract, which has presented high levels of 5-HT_{2A}R mRNA (Pompeiano et al. 1994). In contrast to the pattern of 5-HT_{2A}R immunoreactivity, autoradiographic observations of the binding sites of the 5-HT_2 receptor have demonstrated low receptor levels in the rat superficial amygdaloid nuclei, although the anterior cortical nucleus has shown a high density of binding sites (Pazos et al. 1985).

In the rat superficial nuclei, the 5-HT_{2A}R–IR neurons are heterogeneous in shape and size (Bombardi 2011). Pyramidal neurons are located mainly in the nucleus of the lateral olfactory tract (layer II), the anterior cortical nucleus (layers II and III), the periamygdaloid cortex (layers II and III), and the posterior cortical nucleus (layers II and III) (Bombardi 2011). In these cells, the 5-HT_{2A}R is abundant in apical dendrites, where it may induce excitatory synaptic currents. Small to large nonpyramidal neurons in many superficial nuclei (nucleus of the lateral olfactory tract, anterior cortical nucleus, periamygdaloid cortex, and posterior cortical nucleus) express 5-HT_{2A}Rs (Bombardi 2011). These interneurons are located in all three layers but are particularly abundant in layers II and III (Bombardi 2011). The pattern of 5-HT_{2A}R–IR neurons in the medial nucleus is different from that seen in other superficial amygdaloid nuclei (Bombardi 2011). This is not surprising, since Golgi studies have demonstrated that the cells contained in the medial nucleus were different from the pyramidal and nonpyramidal neurons located in the other superficial nuclei (McDonald 1992, 1998; Sah et al. 2003). In fact, the rat medial nucleus especially contains 5-HT_{2A}R–IR neurons with ovoid somata (Bombardi 2011).

Remaining nuclei

In situ hybridization preparations have reported moderate levels of 5-HT_2R mRNA in the rat central nucleus (Wright et al. 1995). Accordingly, immunohistochemical studies have revealed that the rat central nucleus displays ovoid-shaped somata stained for the 5-HT_{2A}R (Cornea-Hébert et al. 1999; Bombardi 2011). Many 5-HT_{2A}R–IR cells with angular- and ovoid-shaped somata are located in the rat anterior amygdaloid area (Bombardi 2011). Small and large neurons in the rat intercalated nuclei express the 5-HT_{2A}R (Xu and Pandey 2000; Bombardi 2011). This result is in disagreement with in situ hybridization studies, showing that intercalated nuclei do not present 5-HT_{2A}R mRNA (Pompeiano et al. 1994). Finally, pyramidal and nonpyramidal neurons of the rat amygdalohippocampal area contain the 5-HT_{2A}R (Bombardi 2011).

Distribution of the 5-HT_{2A} receptor in the hippocampal region

Hippocampal formation

The presence of the 5-HT_2R or the 5-HT_{2A}R in the hippocampal formation has been demonstrated in different studies. In rat, Wright et al. (1995) demonstrated low, intermediate, and high levels of 5-HT_2R mRNA in the hippocampus proper, subiculum, and DG, respectively. 5-HT_{2A}R transcripts have also been observed in the rat hippocampal formation, particularly in the pyramidal cell layer of the CA3 field (Pompeiano et al. 1994). In contrast to in situ hybridization studies, autoradiographic observations of the binding sites of the 5-HT_2R have demonstrated low receptor levels in the rat hippocampal formation, although the ventral DG has presented an intermediate level of specific binding (Pazos et al. 1985). Immunohistochemical studies have demonstrated that the 5-HT_{2A}R–IR cells in the rat hippocampal formation are morphologically heterogeneous and correspond to excitatory and inhibitory neurons (Cornea-Hébert et al. 1999; Xu and Pandey 2000; Jansson et al. 2001; Lüttgen et al. 2004; Klempin et al. 2010; Bombardi 2012). In particular, it has been demonstrated that virtually all principal excitatory neurons (granule cells and pyramidal cells) of the hippocampal formation express the 5-HT_{2A}R. A strong 5-HT_{2A}R immunoreactivity is localized in the apical dendrite of the pyramidal cells where this serotonin receptor may increase excitatory postsynaptic currents (Lüttgen et al. 2004; Bombardi 2012). The finding that the 5-HT_{2A}R is expressed by hippocampal pyramidal neurons correlates with an electrophysiological study demonstrating that, in the pyramidal somata of the rat CA1 (ventral field), the outward current induced by serotonin and alpha-methyl-serotonin (a 5-HT_2 agonist) is blocked by ketanserin (a 5-HT_2 antagonist) and spiperone (a 5-HT_{1A} and 5-HT_2 antagonist) in a concentration-dependent manner (Uneyama et al. 1992). The 5-HT_{2A}R is also expressed in the rat mossy fibers (Bombardi 2012). It is known that the mossy fibers arise from the granule cells and leave the DG to innervate the pyramidal cells of the CA3 hippocampal field (Amaral and Lavenex 2007). The 5-HT_{2A}R located at presynaptic level could modulate excitatory

neurotransmission in the mossy fibers and consequently act on the hippocampal release of glutamate. This is in agreement with studies indicating that different subtypes of serotonin receptors can affect presynaptic neurotransmission (Hashimoto and Kita 2008; Guo and Rainnie 2010).

Colocalization analysis shows that the majority of GABAergic neurons located in the different areas of the rat hippocampal formation express 5-HT_{2A}R (Bombardi 2012). In the DG, 5-HT_{2A}R is expressed by 91.7 %, of GABAergic interneurons. In the granule cell layer, most of the GABAergic neurons (90.2 %) express 5-HT_{2A}R (Bombardi 2012). Many of these latter cells (91.5 %) are located between the granule cell layer and the polymorphic cell layer. In the polymorphic cell layer, 94.4 % of all GABAergic neurons are 5-HT_{2A}R–IR (Bombardi 2012).

In the hippocampus proper, 90.7 % of the GABAergic neurons express the 5-HT_{2A}R. The colocalization of GABA with 5-HT_{2A}R is similar in the different hippocampal fields (CA1—91.4 %; CA2—89.9 %; CA3—90.4 %). In every hippocampal field, the 5-HT_{2A} receptor is abundantly expressed in a large number of GABAergic interneurons distributed in the pyramidal cell layer (CA1—92.2 %; CA2—91.5 %; CA3—93.7 %), the strata oriens (CA1—97.1 %; CA2—95.5 %; CA3—95.3 %), radiatum (CA1—86.9 %; CA2—84.8 %; CA3—84.4 %), and lacunosum-moleculare (CA1—88.7 %; CA2—89.7 %; CA3—89.1 %) (Bombardi 2012).

In the subiculum, 84.2 % of the GABAergic neurons are 5-HT_{2A}R–IR. These interneurons are present in every layer, but are particularly abundant in the principal cell layer, where the 5-HT_{2A}R is expressed by 91.2 % of GABAergic interneurons. In the molecular layer, only 49.3 % of the GABA–IR neurons express 5-HT_{2A}R (Bombardi 2012).

The presence of the 5-HT_{2A}R in the GABA–IR neurons is in agreement with electrophysiological studies, indicating that 5-$HT_{2A/2C}$ receptors activate GABAergic neurons in the rat DG (Piguet and Galvan 1994) and the rat CA1 field of the hippocampus proper (Shen and Andrade 1998).

In the rat DG, the distribution of GABAergic/5-HT_{2A}R–IR neurons in the deep surface of the granule cell layer resembles the neurogenic gradients (suprapyramidal to infrapyramidal gradient) observed during granule cell ontogenesis (Bayer 1980; Bombardi 2012). In addition, the high density of 5-HT_{2A}R–IR neurons located along the deeper portion of the granule cell layer is in agreement with a study, demonstrating that this serotonin receptor can regulate neurogenesis in the subgranular zone (Jha et al. 2008). Since GABA regulates both the progenitor turnover and the integration of newly generated neurons in the DG (Ge et al. 2006), it is reasonable to assume that the GABAergic neurons distributed in the subgranular zone may be involved in 5-HT_{2A}R-mediated hippocampal progenitor proliferation (Banasr et al. 2004).

In the DG and hippocampus proper, several classifications of GABAergic interneurons have been proposed, based on their morphology, axonal location, neurochemical code, and electrophysiological characteristics (for reviews, see Freund and Buzsáki 1996; Witter and Amaral 2004; Amaral et al. 2007; Amaral and Lavenex 2007). The 5-HT_{2A}R–IR inhibitory interneurons of the DG and hippocampus proper, on the basis of their location, morphology, and neurochemical code, could correspond to specific types of inhibitory interneurons (Lüttgen et al. 2004; Bombardi 2012). In the rat DG, the interneurons expressing the 5-HT_{2A}R may correspond to PV–IR pyramidal basket (located at the border of the granule cell layer with the polymorphic cell layer), PV-immunopositive chandelier (axo-axonic) cells (located within the granule cell layer), and SOM–IR interneurons with hilar dendrites and ascending axons (HIPP cells) (located in the polymorphic cell layer, immediately adjacent to the granule cell layer) (Lüttgen et al. 2004; Bombardi 2012).

In the rat hippocampus proper, the GABAergic interneurons expressing the 5-HT_{2A}R are located in the strata oriens, radiatum, lacunosum-moleculare, and in the pyramidal cell layer. These interneurons may correspond to the following cells: SOM/neuropeptide Y–IR cells terminating in conjunction with entorhinal afferent (O-LM cells) (stratum oriens), calbindin-D28 k (CB)–IR neurons (stratum oriens), CB–IR interneurons with the axon and dendrites in the stratum radiatum (stratum radiatum), VIP–IR IS3 interneurons (stratum radiatum), CB–IR horizontal lacunosum-moleculare interneurons (located at the border of the stratum lacunosum-moleculare with the stratum radiatum and within the stratum lacunosum-moleculare), PV–IR pyramidal basket cells (pyramidal cell layer), and PV–IR chandelier cells (pyramidal cell layer) (Lüttgen et al. 2004; Bombardi 2012).

Parahippocampal region

High density of 5-HT_2R ligand binding sites is present in the rat entorhinal cortex (Pazos et al. 1985). In addition, high levels of 5-HT_{2A}R mRNA levels are located in the rat entorhinal cortex, particularly in layers V and VI (Pompeiano et al. 1994). These data coincide with immunohistochemical studies showing that a variety of morphological cell types is distributed in the rat entorhinal cortex and elsewhere in the rat parahippocampal region (Cornea-Hébert et al. 1999; Bombardi 2012).

Pyramidal or modified pyramidal cells are the main cell type of the rat parahippocampal region expressing 5-HT_{2A}R (Bombardi 2012). This receptor is strongly expressed on the apical dendrite of pyramidal neurons where it could modulate excitatory glutamate input, as has been demonstrated in the cerebral cortex (Puig et al. 2003).

In the rat parahippocampal region, 5-HT_{2A}Rs are also localized in nonpyramidal neurons (Bombardi 2012). In particular, double-immunolabeling analysis has revealed that a majority of the GABAergic cells in the entorhinal cortex contained 5-HT_{2A}Rs. These nonpyramidal neurons are present in every layer, but are abundant in layers II, III, V, and VI, where the 5-HT_{2A}R is expressed by 82.1, 85.3, 93.4, and 92.3 % of interneurons, respectively (Bombardi 2012). The rat entorhinal cortex is divided into six cytoarchitectonically distinct fields: the dorsal lateral entorhinal field (DLE), the dorsal intermediate entorhinal field (DIE), the amygdalo-entorhinal transitional field (AE), the ventral intermediate entorhinal field (VIE), the medial entorhinal field (ME), and the caudal entorhinal field (CE) (Insausti et al. 1997). Interestingly, there is no significant difference in the colocalization pattern of GABA and 5-HT_{2A}Rs in the different fields of the entorhinal cortex (DLE 86.7 %; DIE 85.6 %; AE 74.9 %; VIE 87.4 %; ME 84.7 %; CE 92.3 %) (Bombardi 2012).

Implication of the cellular distribution of the 5-HT_{2A} receptor in amygdalar and hippocampal microcircuits

Microcircuits located in the amygdala and hippocampal region consist of principal (excitatory) neurons and GABAergic (inhibitory) interneurons which can exert inhibitory control of the soma, proximal dendrites, distal dendrites, and the initial axonal segment of the principal cells (Aggleton 2000; Witter and Amaral 2004; Amaral et al. 2007; Amaral and Lavenex 2007; Whalen and Phelps 2009). From available data, it is possible to conclude that 5-HT_{2A}Rs are located on both the excitatory and the inhibitory neurons of the amygdala and hippocampal region. Therefore, serotonin modulates the activity of the principal cells in various ways, either directly through the activation of the 5-HT_{2A}R in the principal cells or indirectly through the activation of the 5-HT_{2A}R in the GABAergic neurons.

The exact knowledge of the role of the 5-HT_{2A}R located in the principal cells of the amygdala and hippocampal region is virtually inexistent. However, the 5-HT_{2A}R present in pyramidal cells of the deep nuclei could increase cell firing and synaptic plasticity, as reported by Stein et al. (2000) and Chen et al. (2003), respectively. Similarly, pyramidal cells of the hippocampal region could be excited through the activation of the 5-HT_{2A}R, as reported in pyramidal cells of the ventral CA1 field (Uneyama et al. 1992).

Electrophysiological studies have demonstrated that the 5-$HT_{2A/2C}$Rs activate GABAergic neurons in the deep amygdalar nuclei (Rainnie 1999; Stutzmann and LeDoux 1999; Stein et al. 2000; Sokal et al. 2005; Jiang et al. 2008),

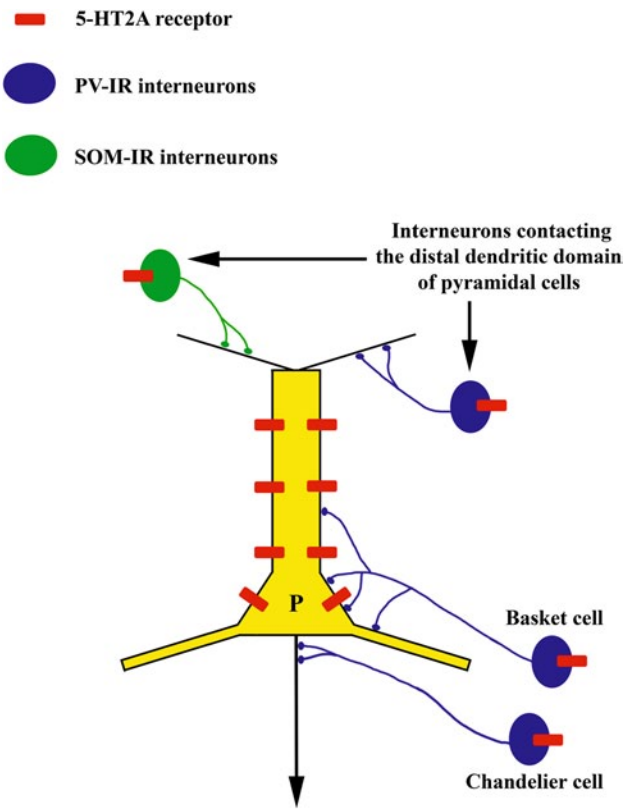

Fig. 1 Schematic drawing of a neuronal microcircuit expressing 5-HT_{2A} receptors (5-HT_{2A}Rs) in the basolateral amygdala. 5-HT_{2A}Rs are located in pyramidal cells (P) and also in GABAergic nonpyramidal interneurons containing parvalbumin (PV) or somatostatin (SOM). PV-immunoreactive (IR) interneurons are basket or chandelier cells. However, PV–IR interneurons can also provide an extensive innervation of distal dendrites of pyramidal cells. SOM–IR interneurons contact distal dendritic domain of pyramidal cells

in the DG (Piguet and Galvan 1994), and the CA1 field of the hippocampus proper (Shen and Andrade 1998).

In the deep amygdaloid nuclei, the GABAergic nonpyramidal neurons expressing 5-HT_{2A}Rs contain especially PV, but also SOM (McDonald and Mascagni 2007; Fig. 1). At the electron microscope level, PV–IR axon terminals form symmetrical synapses with a variety of postsynaptic elements, which include perisomatic (cell body, axon initial segment, and thick proximal dendrites) and distal dendritic (small-caliber dendrites and dendritic spines) domains of pyramidal cells (Muller et al. 2006; Fig. 1). The PV–IR neurons are connected by gap junctions and constitute an inhibitory network that synchronizes the firing of pyramidal cells (Woodruff and Sah 2007). Since most of the pyramidal neurons form intimate synapse-like contacts with the perisomatic domain of the PV–IR interneurons, the activities of these two cell types are regulated by reciprocal circuit (McDonald et al. 2005). This reciprocal perisomatic connection may be important to modulate the

synchronized rhythmic activity associated with the formation of emotional memories (Paré and Collins 2000; Paré et al. 2002; Rainnie et al. 2006).

In the deep nuclei, SOM–IR neurons provide an inhibitory innervation (symmetrical synapses) especially of distal dendritic domain (small-caliber dendrites and dendritic spines) of pyramidal cells (Muller et al. 2007a; Fig. 1). Since SOM–IR axon terminals are adjacent to asymmetrical excitatory glutamatergic synapses involved in emotional memories, the SOM–IR interneurons could play a critical role in the modulation of synaptic plasticity occurring in the distal dendritic domain of pyramidal cells related to emotional learning (Paré et al. 2002; Muller et al. 2007a).

Together, these data indicate that 5-HT_{2A}R–IR GABAergic interneurons in the deep nuclei could regulate the genesis of emotional memories acting on different domains of pyramidal cells.

In the hippocampal formation, 5-HT_{2A}Rs could be expressed by GABAergic interneurons which innervate the cell body and proximal dendrites (PV–IR basket cells), the proximal dendrites (CB–IR interneurons), the initial axonal segment (PV–IR chandelier or axo-axonic cells), and the distal dendrites (SOM–IR HIPP cells; SOM–IR O-LM cells; CB–IR interneurons located in the strata radiatum and lacunosum-moleculare) of the principal cells (granule and pyramidal cells; Figs. 2, 3). Furthermore, 5-HT_{2A}R could be located also in VIP–IR interneurons contacting other interneurons (Lüttgen et al. 2004; Bombardi 2012; Figs. 2, 3).

In the hippocampus formation, the GABAergic interneurons targeting the perisomatic and distal dendritic domains of the pyramidal cells can modulate the firing and the synaptic plasticity of the principal cells, respectively. Thus, these interneurons could be involved in the hippocampal synchronization related to learning and memory (Maccaferri and Lacaille 2003; Klausberger and Somogyi 2008; Ellender and Paulsen 2010). This indicates that activation of 5-HT_{2A}Rs in hippocampal GABAergic interneurons may have effects on the formation of memories

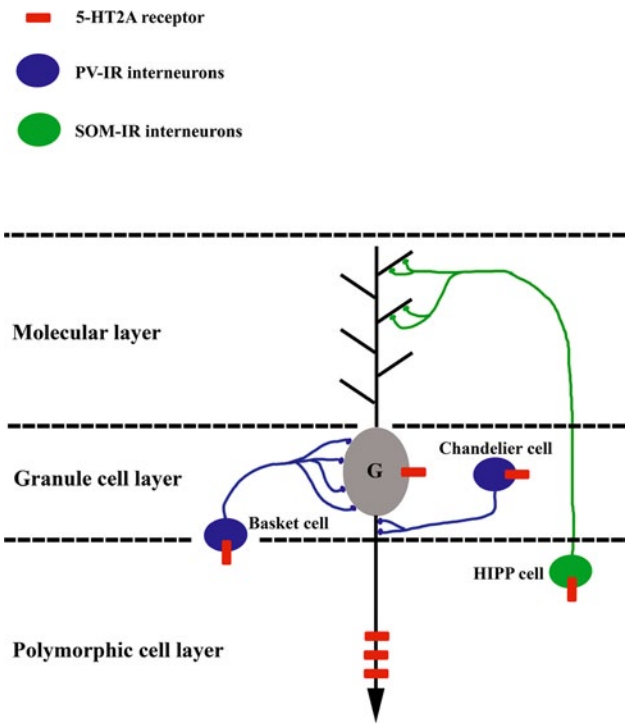

Fig. 2 Schematic drawing of a neuronal microcircuit expressing 5-HT_{2A} receptors (5-HT_{2A}Rs) in the dentate gyrus (DG). 5-HT_{2A}Rs are expressed on both the excitatory (granule cells, G) and the inhibitory interneurons. 5-HT_{2A}R-immunoreactive (IR) inhibitory interneurons express parvalbumin (PV) or somatostatin (SOM). PV–IR interneurons are basket or chandelier cells, whereas SOM–IR interneurons contact distal dendrites of granule cells and may be identified as interneurons with hilar dendrites and ascending axons (HIPP cells). Interestingly, 5-HT_{2A}Rs are also expressed in the mossy fibers

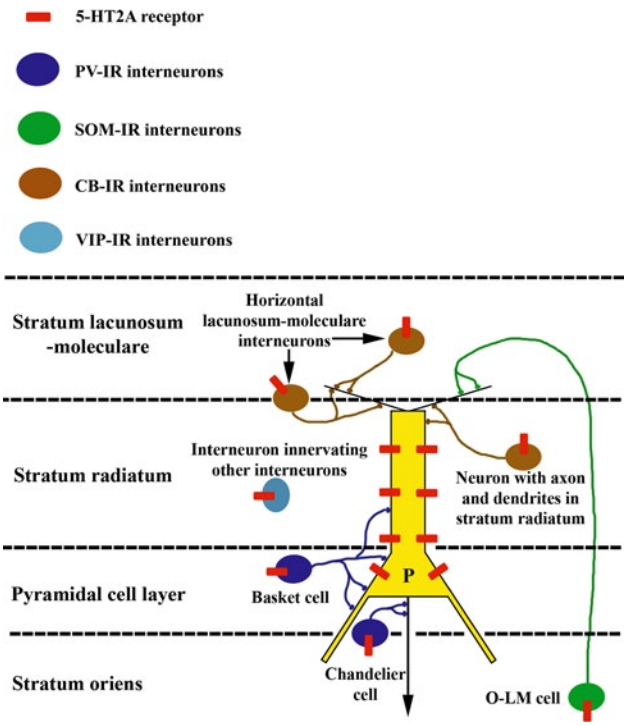

Fig. 3 Schematic drawing of a neuronal microcircuit expressing 5-HT_{2A} receptors (5-HT_{2A}Rs) in the hippocampus proper. 5-HT_{2A}Rs are located in excitatory (pyramidal cells, P) as well as inhibitory neurons. In particular, 5-HT_{2A}R could be expressed by GABAergic interneurons which innervate the cell body and proximal dendrites (parvalbumin-immunoreactive [IR] basket cells), the proximal dendrites (calbindin-D28 k-IR interneurons), the initial axonal segment (parvalbumin-IR chandelier cells), and the distal dendrites (somatostatin-IR O-LM cells; calbindin-D28 k-IR interneurons) of the pyramidal cells. Furthermore, 5-HT_{2A}Rs could be expressed also in vasoactive intestinal peptide-IR interneurons contacting other interneurons

associated with synchronous activity of the hippocampal principal cells. Consistent with this finding, M100907, a highly selective 5-HT_{2A}R antagonist, enhances theta activity in the rodent hippocampus (Kehne et al. 1996). Accordingly, M100907 application to brain slices facilitates the induction of long-term potentiation (LTP) within the CA1 field of the rat hippocampus proper (Wang and Arvanov 1998).

Role of 5-HT_{2A}RS on amygdala/hippocampus interaction in emotional memories

Emotion and memory are closely related. Impaired regulation of emotional memory is a feature of several affective disorders, including depression, anxiety, and post-traumatic stress disorder (PTSD). Converging findings of animal and human studies provide compelling evidence that emotion-associated modulation of memories occurs, in part, by interactions between the basolateral amygdala (BLA) and the hippocampus (Richardson et al. 2004; Tsoory et al. 2008). Emotional conditions might induce long-term neural plasticity in the amygdala, and therefore the interrelations between the amygdala and the hippocampus are not static but dynamic (Richter-Levin 2004). The role of 5-HT_{2A}Rs in the functional interaction between these two areas has not yet been fully investigated. BLA contributes to modulation of hippocampal LTP (Abe et al. 2003), and intra-BLA injection of 5-HT_2R antagonists and agonists inhibits and promotes the induction of perforant path-DG LTP, respectively (Abe et al. 2009). Although these authors claimed that these effects were mediated by 5-HT_{2C}Rs, they did not use selective antagonists, for example, SB242084 (Di Matteo et al. 2000) leaving doubts about the receptor subtype involved. Recently, it has been shown that stimulation of 5-HT_{2A}Rs facilitates the consolidation and extinction of trace and delay cued fear memory and the consolidation of object memory in mice (Zhang et al. 2013). Blocking 5-HT_{2A}Rs impairs the acquisition of fear memory extinction. These results support the view that serotonergic activation of the 5-HT_{2A}Rs provides an important modulatory influence on circuits engaged during extinction learning (Zhang et al. 2013). It is also possible that 5-HT_{2A}Rs are involved in hippocampal cytoskeletal protein (Arc) increase induced by BLA activation (McIntyre et al. 2005) since early evidence has shown that DOI modulates activation of hippocampal immediate early genes (Tilakaratne and Friedman 1996). Furthermore, 5-HT_{2A}R might mediate BLA-induced adult hippocampal neurogenesis in fear context-specific activation (Kirby et al. 2012). Indeed, it is known that 5-HT_{2A}R activation increases adult neurogenesis similar to antidepressants (Banasr et al. 2004).

Concluding remarks

The present review reported that, in the amygdala and hippocampal region, 5-HT_{2A}Rs are located on both excitatory and inhibitory neurons. Thus, this receptor, modulating the activity of amygdalar and hippocampal microcircuits, could be critically involved in the regulation of emotional processes and cognitive functions. Moreover, 5-HT_{2A} receptor signaling may be a critical link in the pathogenesis of anxiety and cognitive impairment seen in different disorders. The evidence reviewed here suggests that genetic influences on serotonergic systems and 5-HT_{2A}Rs might contribute to individual differences in the emotional memory process. Given that the association between serotonin and anxiety such as panic disorders and PTSD has been strongly demonstrated in the literature and is considered to have a heritable foundation, 5-HT_{2A} hypofunction could represent a neurochemical trait that predisposes individuals to anxiety and impaired regulation of emotional memory, typical features of affective disorders.

Pharmacotherapy tailored to modulating the effect of 5-HT_{2A} in the amygdala and hippocampus thus might represent an important future direction in developing novel, more efficacious, pharmacological agents for the symptoms associated with anxiety and fear-related memory disorders. Nevertheless, the functional significance of the 5-HT_{2A}Rs in these regions remains controversial and necessitates additional clarifications.

References

Abe K, Niikura Y, Misawa M (2003) The induction of long-term potentiation at amygdalo-hippocampal synapses in vivo. Biol Pharm Bull 26:1560–1562

Abe K, Fujimoto T, Akaishi T, Misawa M (2009) Stimulation of basolateral amygdaloid serotonin 5-HT(2C) receptors promotes the induction of long-term potentiation in the dentate gyrus of anesthetized rats. Neurosci Lett 451:65–68

Aggleton JP (2000) The amygdala: a functional analysis, 2nd edn. Oxford University Press, New York

Amaral DG, Lavenex P (2007) Hippocampal neuroanatomy. In: Andersen P, Morris R, Amaral D, Bliss T, O'Keefe J (eds) The hippocampus book. Oxford University Press, New York, pp 37–114

Amaral DG, Scharfman HE, Lavenex P (2007) The dentate gyrusDG: fundamental neuroanatomical organization (dentate gyrus for dummies). Prog Brain Res 163:3–22

Banasr M, Hery M, Printemps R, Daszuta A (2004) Serotonin-induced increases in adult cell proliferation and neurogenesis are mediated through different and common 5-HT receptor subtypes in the dentate gyrus and the subventricular zone. Neuropsychopharmacology 29:450–460

Barnes NM, Sharp T (1999) A review of central 5-HT receptors and theirs function. Neuropharmacology 38:1083–1152

Bauman MD, Amaral DG (2005) The distribution of serotoninergic fibers in the macaque monkey amygdala: an immunohistochemical study using antisera to 5-hydroxytriptamine. Neuroscience 136:193–203

Bayer SA (1980) Development of the hippocampal region in the rat. I. Neurogenesis examined with ^{3}H-thymidine autoradiography. J Comp Neurol 190:87–114

Bombardi C (2011) Distribution of 5-HT2A receptor immunoreactivity in the rat amygdaloid complex and colocalization with γ-aminobutyric acid. Brain Res 1370:112–128

Bombardi C (2012) Neuronal localization of 5-HT2A receptor immunoreactivity in the rat hippocampal region. Brain Res Bull 87:259–273

Chen A, Hough J, Li H (2003) Serotonin type II receptor activation facilitates synaptic plasticity via N-Methyl-D-Aspartate-mediated mechanism in the rat basolateral amygdala. Neuroscience 119:53–63

Cornea-Hébert V, Riad M, Wu C, Singh SK, Descarries L (1999) Cellular end subcellular distribution of the serotonin 5-HT2A receptor in the central nervous system of adult rat. J Comp Neurol 409:187–209

de Quervain DJ, Henke K, Aerni A, Coluccia D, Wollmer MA, Hock C, Nitsch RM, Papassotiropoulos A (2003) A functional genetic variation of the 5-HT2A receptor affects human memory. Nat Neurosci 6:1141–1142

Di Giovanni G, Di Matteo V, Pierucci M, Benigno A, Esposito E (2006) Central serotonin2c receptor: from physiology to pathology. Curr Top Med Chem 6:1909–1925

Di Giovanni G, Esposito E, Di Matteo V (eds) (2011) 5-HT2C receptors in the pathophysiology of CNS disease. Springer, New York

Di Matteo V, Di Giovanni G, Esposito E (2000) SB 242084: a selective 5-HT(2C) receptor antagonist. CNS Drugs Rev 3: 195–205

Eichenbaum H, Schoenbaum G, Young B, Bunsey M (1996) Functional organization of the hippocampal memory system. Proc Natl Acad Sci USA 93:13500–13507

Ellender TJ, Paulsen O (2010) The many tunes of perisomatic targeting interneurons in the hippocampal network. Front Cell Neurosci 4:1–26

Esposito E, Di Matteo V, Di Giovanni G (2008) Serotonin-dopamine interaction: an overview. Prog Brain Res 172:3–6

Freund TF, Buzsáki G (1996) Interneurons of the hippocampus. Hippocampus 6:347–470

Ge S, Goh ELK, Sailor KA, Kitabatake Y, Ming G, Song H (2006) GABA regulates synaptic integration of newly generated neurons in the adult brain. Nature 439:589–593

Graeff FG, Zangrossi H Jr (2010) The dual role of serotonin in defense and the mode of action of antidepressants on generalized anxiety and panic disorders. Cent Nerv Syst Agents Med Chem 10:207–217

Gray JA, Roth BL (2001) Paradoxical trafficking and regulation of 5-HT2A receptors by agonists and antagonists. Brain Res Bull 56:441–451

Guo JD, Rainnie DG (2010) Presynaptic 5-HT1B receptor-mediated serotonergic inhibition of glutamate transmission in the bed nucleus of the stria terminalis. Neuroscience 165:1390–1401

Harvey JA (2003) Role of the serotonin 5-HT(2A) receptor in learning. Learn Mem 10:355–362

Hashimoto K, Kita H (2008) Serotonin activates presynaptic and postsynaptic receptors in rat globus pallidus. J Neurophysiol 99:1723–1732

Hensler JG (2006) Serotonergic modulation of the limbic system. Neurosci Biobehav Rev 30:203–214

Hoyer D, Hannon JP, Martin GR (2002) Molecular, pharmacological and functional diversity of 5-HT receptors. Pharmacol Biochem Behav 71:533–554

Hurlemann R, Schlaepfer TE, Matusch A, Reich H, Shah NJ, Zilles K, Maier W, Bauer A (2009) Reduced 5-HT(2A) receptor signaling following selective bilateral amygdala damage. Soc Cogn Affect Neurosci 4:79–84

Insausti R, Herrero MT, Witter MP (1997) Entorhinal cortex of the rat: cytoarchitectonic subdivisions and the origin and distribution of cortical efferents. Hippocampus 7:146–183

Jansson A, Tinner B, Bancila M, Vergé D, Steinbusch HWM, Agnati LF, Fuxe K (2001) Relationships of 5-hydroxytryptamine immunoreactive terminal-like varicosities to 5- hydroxytryptamine-2A receptor-immunoreactive neuronal processes in the rat forebrain. J Chem Neuroanat 22:185–203

Jha S, Rajendran R, Fernandes KA, Vaidya VA (2008) 5-HT2A/2C receptor blockade regulates progenitor cell proliferation in the adult rat hippocampus. Neurosci Lett 441:210–214

Jiang X, Xing G, Yang C, Verma A, Zhang L, Li H (2008) Stress impairs 5-HT2A Receptor-mediated serotonergic facilitation of GABA release in juvenile rat basolateral amygdala. Neuropsychopharmacology 33:1–14

Kehne JH, Baron BM, Carr AA, Chaney SF, Elands J, Feldman DJ, Frank RA, van Giersbergen PL, McCloskey TC, Johnson MP, McCarty DR, Poirot M, Senyah Y, Siegel BW, Widmaier C (1996) Preclinical characterization of the potential of the putative atypical antipsychotic MDL 100,907 as a potent 5-HT2A antagonist with a favourable CNS safety profile. J Pharmacol Exp Ther 277:968–981

Kemppainen S, Jolkkonen E, Pitkänen A (2002) Projections from the posterior cortical nucleus of the amygdala to the hippocampal formation and the parahippocampal region in rat. Hippocampus 12:735–755

Kirby ED, Friedman AR, Covarrubias D, Ying C, Sun WG, Goosens KA, Sapolsky RM, Kaufer D (2012) Basolateral amygdala regulation of adult hippocampal neurogenesis and fear-related activation of newborn neurons. Mol Psychiatry 17:527–536

Klausberger T, Somogyi P (2008) Neuronal diversity and temporal dynamics: the unity of hippocampal circuit operations. Science 321:53–57

Klempin F, Babu H, De Pietri TD, Alarcon E, Fabel K, Kempermann G (2010) Oppositional effects of serotonin receptors 5-HT1a, 2, and 2c in the regulation of adult hippocampal neurogenesis. Front Mol Neurosci 3:1–11

LaBar KS, Phelps EA (1998) Role of the human amygdala in arousal mediated memory consolidation. Psych Sci 9:490–493

Lopez-Gimenez JF, Vilaro MT, Palacios JM, Mengod G (2001) Mapping of 5-HT2A receptors and their mRNA in monkey brain: [3H]MDL100,907 autoradiography and in situ hybridization studies. J Comp Neurol 429:571–589

Lüttgen M, Ögren SO, Meister B (2004) Chemical identity of 5-HT_{2A} receptor immunoreactive neurons of the rat septal complex and dorsal hippocampus. Brain Res 1010:156–165

Maccaferri G, Lacaille JC (2003) Interneuron Diversity series: hippocampal interneuron classifications–making things as simple as possible, not simpler. Trends Neurosci 26:564–571

Majak K, Pitkänen A (2003) Projections from the periamygdaloid cortex to the amygdaloid complex, the hippocampal formation, and the parahippocampal region: a PHA-L study in the rat. Hippocampus 13:922–942

McDonald AJ (1992) Cells types and intrinsic connections of the amygdala. In: Aggleton JP (ed) The amygdala: neurobiological aspects of emotion, memory and mental dysfunction. Wiley-Liss, New York, pp 67–96

McDonald AJ (1998) Cortical pathways to the mammalian amygdala. Prog Neurobiol 55:257–332

McDonald AJ, Mascagni F (2007) Neuronal localization of 5-HT type 2A receptor immunoreactivity in the rat basolateral amygdala. Neuroscience 146:306–320

McDonald AJ, Mascagni F, Mania I, Rainnie D (2005) Evidence for a perisomatic innervation of parvalbumin-containing interneurons by individual pyramidal cells in the basolateral amygdala. Brain Res 1035:32–40

McIntyre CK, Miyashita T, Setlow B, Marjon KD, Steward O, Guzowski JF et al (2005) Memory-influencing intra-basolateral amygdala drug infusions modulate expression of Arc protein in the hippocampus. Proc Natl Acad Sci USA 102:10718–10723

Meltzer HY, Huang M (2008) In vivo actions of atypical antipsychotic drug on serotonergic and dopaminergic systems. Prog Brain Res 172:177–197

Mintun MA, Sheline YI, Moerlein SM, Vlassenko AG, Huang Y, Snyder AZ (2004) Decreased hippocampal 5-HT2A receptor binding in major depressive disorder: in vivo measurement with [18F]altanserin positron emission tomography. Biol Psychiatry 55:217–224

Morilak DA, Garlow SJ, Ciaranello RD (1993) Immunocytochemical localization and description of neurons expressing serotonin$_2$ receptors in the rat brain. Neuroscience 54:701–717

Morris R (2007) Theories of hippocampal function. In: Andersen P, Morris R, Amaral D, Bliss T, O'Keefe J (eds) The hippocampus book. Oxford University Press, New York, pp 581–694

Muller JF, Mascagni F, McDonald AJ (2006) Pyramidal cells of the rat basolateral amygdala: synaptology and innervation by parvalbumin-immunoreactive interneurons. J Comp Neurol 494:635–650

Muller JF, Mascagni F, McDonald AJ (2007a) Postsynaptic targets of somatostatin-containing interneurons in the rat basolateral amygdala. J Comp Neurol 500:513–529

Muller JF, Mascagni F, McDonald AJ (2007b) Serotonin-immunoreactive axon terminals innervate pyramidal cells and interneurons in the rat basolateral amygdala. J Comp Neurol 505:314–335

Paré D, Collins DR (2000) Neuronal correlates of fear in the lateral amygdala: multiple extracellular recordings in conscious cats. J Neurosci 16:3334–3350

Paré D, Collins DR, Pelletier JG (2002) Amygdala oscillations and the consolidation of emotional memories. Trends Cogn Sci 6:306–314

Pazos A, Cortés R, Palacios JM (1985) Quantitative autoradiographic mapping of serotonin receptors in the rat brain. II. Serotonin-2 receptors. Brain Res 346:231–249

Phelps EA (2004) Human emotion and memory: interactions of the amygdala and hippocampal complex. Curr Opin Neurobiol 14:198–202

Piguet P, Galvan M (1994) Transient and long-lasting actions of 5-HT on rat dentate gyrus neurones in vitro. J Physiol 481: 629–639

Pikkarainen M, Pitkänen A (2001) Projections from the lateral, basal and accessory basal nuclei of the amygdala to the perirhinal and postrhinal cortices in rat. Cereb Cortex 11:1064–1082

Pikkarainen M, Ronkko S, Savander V, Insausti R, Pitkänen A (1999) Projections from the lateral, basal, and accessory basal nuclei of the amygdala to the hippocampal formation in rat. J Comp Neurol 403:229–260

Pitkänen A (2000) Connectivity of the rat amygdaloid complex. In: Andersen P, Morris R, Amaral D, Bliss T, O'Keefe J (eds) The hippocampus book. Oxford University Press, New York, pp 31–115

Pitkänen A, Kemppainen S (2002) Comparison of the distribution of calcium-binding proteins and intrinsic connectivity in the lateral nucleus of the rat, monkey, and human amygdala. Pharmacol Biochem Behav 71:369–377

Pitkänen A, Kelly JL, Amaral DG (2002) Projections from the lateral, basal, and accessory basal nuclei of the amygdala to the entorhinal cortex in the macaque monkey. Hippocampus 12:186–205

Pompeiano M, Palacios JM, Mengod G (1994) Distribution of serotonin 5-HT$_2$ receptor family mRNAs: comparison between 5-HT$_{2A}$ and 5-HT$_{2C}$ receptors. Mol Brain Res 23:163–178

Pralong E, Magistretti P, Stoop R (2002) Cellular perspectives on the glutamate-monoamine interactions in limbic lobe structures and their relevance for some psychiatric disorders. Prog Neurobiol 67:173–202

Puig MV, Celada P, Díaz-Mataiax L, Artigias F (2003) In vivo modulation of the activity of pyramidal neurons in the rat medial prefrontal cortex by 5-HT2A receptors. Relationship to thalamocortical afferents. Cereb Cortex 13:1870–1882

Rainnie DG (1999) Serotoninergic modulation of neurotransmission in the rat basolateral amygdala. J Neurophysiol 82:69–85

Rainnie DG, Mania I, Mascagni F, McDonald AJ (2006) Physiological and morphological characterization of parvalbumin-containing interneurons of the rat basolateral amygdala. J Comp Neurol 498:142–161

Regina MJ, Bucelli RC, Winter JC, Rabin RA (2004) Cellular mechanism of serotonin 5-HT$_{2A}$ receptor-mediated cGMP formation: the essential role of glutamate. Brain Res 1003:168–175

Richardson MP, Strange BA, Dolan RJ (2004) Encoding of emotional memories depends on amygdala and hippocampus and their interactions. Nat Neurosci 7:278–285

Richter-Levin G (2004) The amygdala, the hippocampus, and emotional modulation of memory. Neuroscientist 10:31–39

Sah P, Faber ES, Lopez De Armentia M, Power J (2003) The amygdaloid complex: anatomy and physiology. Physiol Rev 83:803–834

Scharfman HE, Witter MP, Schwarcz R (2000) The parahippocampal region Implications for neurological and psychiatric diseases. Introduction Ann NY Acad Sci 911:ix–xiii

Shen R-Y, Andrade R (1998) 5-hydroxytryptamine 2 receptor facilitates GABAergic neurotransmission in rat hippocampus. J Pharmacol Exp Ther 285:805–812

Shin LM, Rauch SL, Pitman RK (2006) Amygdala, medial prefrontal cortex, and hippocampal function in PTSD. Ann NY Acad Sci 1071:67–79

Sokal DM, Giarola AS, Large CH (2005) Effects of GABA$_B$, 5-HT$_{1A}$, and 5-HT$_2$ receptor stimulation on activation and inhibition of the rat lateral amygdala following medial geniculate nucleus stimulation in vivo. Brain Res 1031:141–150

Spampanato J, Polepalli J, Sah P (2011) Interneurons in the basolateral amygdala. Neuropharmacology 60:765–773

Stein C, Davidowa H, Albrecht D (2000) 5-HT$_{1A}$ receptor-mediated inhibition and 5-HT$_2$ as well as 5-HT$_3$ receptor-mediated excitation in different subdivisions of the rat amygdala. Synapse 38:328–337

Steinbusch HWM (1981) Distribution of serotonin-immunoreactivity in the central nervous system of the rat cell bodies and terminals. Neuroscience 6:557–618

Stutzmann GE, LeDoux JE (1999) GABAergic antagonist block the inhibitory effects of serotonin in the lateral amygdala: a mechanism for modulation of sensory inputs related to fear conditioning. J Neurosci 19:1–4

Tilakaratne N, Friedman E (1996) Genomic responses to 5-HT1A or 5-HT2A/2C receptor activation is differentially regulated in four regions of rat brain. Eur J Pharmacol 307:211–217

Tsoory MM, Vouimba RM, Akirav I, Kavushansky A, Avital A, Richter-Levin G (2008) Amygdala modulation of memory-related processes in the hippocampus: potential relevance to PTSD. Prog Brain Res 167:35–51

Uneyama H, Munakata M, Akaike N (1992) 5-HT response of rat hippocampal pyramidal cell bodies. NeuroReport 3:633–636

Wang RY, Arvanov VL (1998) M100907, a highly selective 5-HT2A receptor antagonist and potential atypical antipsychotic drug, facilitates induction of long-term potentiation in area CA1 of the rat hippocampal slice. Brain Res 779:309–313

Whalen PJ, Phelps EA (2009) The human amygdala. The Guilford Press, New York

Witter MP, Amaral DG (2004) Hippocampal formation. In: Paxinos G (ed) The rat nervous system. Elsevier Academic Press, San Diego, pp 635–704

Woodruff AR, Sah P (2007) Network of parvalbumin-positive interneurons in the basolateral amygdala. J Neurosci 27: 553–563

Wright DE, Seroogy KB, Lundgren KH, Davis BM, Jennes L (1995) Comparative localization of serotonin$_{1A,1C}$, and$_2$ receptor subtype mRNAs in rat brain. J Comp Neurol 351:357–373

Xu T, Pandey SC (2000) Cellular localization of serotonin$_{2A}$ (5-HT$_{2A}$) receptors in the rat brain. Brain Res Bull 51:499–505

Zhang G, Ásgeirsdóttir HN, Cohen SJ, Munchow AH, Barrera MP, Stackman RW Jr (2013) Stimulation of serotonin 2A receptors facilitates consolidation and extinction of fear memory in C57BL/6 J mice. Neuropharmacology 64:403–413